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Evaluating the efficacy of secondary transurethral resection of the bladder for high-grade Ta tumors

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Purpose: The need for secondary transurethral resection of the bladder (re-TURB) in patients with high-grade Ta tumors has not been assessed. This study aimed to compare the outcomes of patients with high-grade Ta tumors who did and did not undergo re-TURB.

Materials and Methods: This study used data from the Seoul National University Prospectively Enrolled Registry for Urothelial Cancer–Transurethral Bladder Tumor Resection (SUPER-UC-TURB). Patients with high-grade Ta tumors who underwent TURB between March 2016 and December 2019 were included. Following the initial TURB, if the pathology results showed a tumor grade higher than high-grade Ta, re-TURB was performed according to the surgeon's recommendation. The recurrence-free survival rate was assessed by Kaplan–Meier analysis and Cox regression analysis between patients who did and did not undergo re-TURB.

Results: In total, 187 patients with high-grade Ta who underwent initial TURB were included, of whom 115 underwent re-TURB and 72 did not. Patients in the re-TURB group had a significantly higher 2-year recurrence-free survival rate than did those in the no re-TURB group (81.3% vs. 60.1%; p=0.005). Whether patients underwent re-TURB was a significant predictor of the risk of bladder cancer recurrence in both the univariate (HR, 0.52; 95% CI, 0.27–0.98; p=0.044) and multivariate (HR, 0.41; 95% CI, 0.19–0.97; p=0.041) analysis.

Conclusions: The risk for bladder cancer recurrence was increased, and the 2-year recurrence-free survival was significantly decreased, in patients with high-grade Ta tumors who did not undergo re-TURB. Thus, re-TURB is beneficial in patients with high-grade Ta bladder cancer.

Keywords: Recurrence; Survival rate; Urinary bladder neoplasms

INTRODUCTION

Bladder cancer is the seventh most common cancer in men and the tenth most common cancer in both sexes worldwide. The age-standardized incidence and mortality are higher in men than in women. The age-standardized incidence (per 100,000 persons/year) is 9.5 in men and 2.4 in women, and the age-standardized mortality (per 100,000 persons/year) is 3.3 in men and 0.86 in women [1-3]. Bladder cancer is categorized into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) depending on the degree of bladder wall involvement. Approximately 75% to 85% and 10% to 15% of cases are NMIBC and MIBC, respectively [4,5].

The 10-year cancer-specific survival rate for high-grade NMIBC (pTa/pT1) is approximately 70% to 85% [6]. The ini-

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tial treatment for NMIBC involves lesion removal by complete transurethral resection of the bladder (TURB). Treatment for NMIBC differs in various risk groups. Patients with T1, Tis, or high-grade Ta tumors with at least two clinical risk factors (age, tumor size, and number of tumors) are considered high-risk and are recommended to undergo intravesical bacille Calmette–Guérin (BCG) instillation. Patients with high-grade Ta tumors with Tis and clinical risk factors (high-grade Ta and Tis with all three risk factors, high-grade T1 and Tis with at least one risk factor, and high-grade T1 without Tis with all three risk factors) are considered very high-risk, and radical cystectomy may be considered after discussion with the patient [7]. The European Association of Urology (EAU) guidelines recommend secondary TURB (re-TURB) within 2 to 6 weeks for T1 or if pathologic findings show incomplete resection; however, the need for re-TURB in patients with high-grade Ta tumors has not been specified [7]. The American Urological Association (AUA) guideline recommends re-TURB for T1 or incomplete resection with an evidence strength grade of B (strong recommendation) and for high-grade Ta tumors with an evidence strength grade of C (moderate recommendation). The 5-year progression-free survival rates of patients with T1 tumors are 88% and 79% for low-grade and high-grade tumors, respectively, and approximately 50% of cases that are initially staged as high-grade T1 are subsequently pathologically upstaged [8,9]. With carcinoma *in situ*, as the progression rate exceeds 70%, the prognosis worsens [10]. Thus, re-TURB is recommended for high-grade T1 tumors to check for potential invasive lesions, even if the pathologic specimen includes the proper muscle layer.

Approximately 75% of Ta tumors are low-grade, and 25% are high-grade. Low-grade Ta tumors have a high recurrence rate of 55% but a progression rate of approximately 5% to 20%. In contrast, 30% to 35% of high-grade Ta tumors subsequently progress to T1 or more severe lesions [11,12]. Considering the prognosis of high-grade tumors, the AUA guidelines recommend re-TURB for high-grade Ta tumors even if the pathology specimen contains the proper muscle layer for a more accurate pathologic diagnosis [7].

Therefore, there is little evidence supporting the need for re-TURB for high-grade Ta tumors, and the strength of recommendation is low. At our hospital, re-TURB was not performed in cases of high-grade Ta tumors based on the surgeon's decision; therefore, we were able to compare cases that underwent re-TURB with those that did not. Therefore, we compared patients with high-grade Ta tumors who did and did not undergo re-TURB, in order to understand the clinical rationale for re-TURB in patients with high-grade Ta tumors.

MATERIALS AND METHODS

1. Study population

The study was approved by Institutional Review Board of the Seoul National University Hospital (approval number: 2106-181-1230), and the informed consent was waived. This study retrospectively analyzed the prospectively collected data of patients registered in the Seoul National University Prospectively Enrolled Registry for Urothelial Cancer–Transurethral Bladder Tumor Resection (SUPER-UC-TURB) [13]. Among 1,220 patients who underwent TURB between March 2016 and December 2019, patients with pathologic Ta high-grade cancer were included. Patients with a history of upper-tract urothelial carcinoma or who underwent immediate cystectomy after TURB were excluded. Finally, 187 patients were included in the analysis, 115 and 72 of whom were included in the re-TURB and no re-TURB groups, respectively. In the re-TURB patient group, postoperative pathology results were also analyzed. Tumors were classified and graded according to the World Health Organization (WHO) classification (2004) by our pathologic institute.

2. Surgical technique

Patients underwent complete TURB with a resectoscope under general or spinal anesthesia. Immediately after TURB, all tumors were depicted by the surgeon on a bladder map, which recorded the tumor site, size, and number. Patients stayed in the hospital until the first day after surgery with continuous irrigation until the next day and were discharged after Foley removal. Patients visited the outpatient clinic 10 to 14 days after the operation. re-TURB was performed according to the clinician's preference within 2 to 6 weeks after the initial TURB. Patients were followed up with cystoscopy every 3 months, and newly diagnosed tumors were considered as recurrence.

3. Statistical analysis

We used SPSS (version 22.0; IBM Corp., Armonk, NY, USA) to analyze the recurrence-free survival (RFS) rate in each group by Kaplan–Meier analysis and Cox regression analysis. Categorical data were compared by using the chi-square test, and quantitative variables were compared by using the t-test (level of significance 0.05).

RESULTS

From March 2016 to December 2019, a total of 187 pa-

tients with high-grade Ta tumors underwent initial TURB. Of these patients, 115 underwent re-TURB and 72 did not. The no re-TURB group consisted of 64 males (88.9%) and 8 females (11.1%), and the re-TURB group consisted of 99 males (86.1%) and 16 females (13.9%). There was no significant difference in the sex ratio between the two groups (p=0.577). There were more older participants in the no re-TURB group, with 28 patients (38.9%) aged under 70 years and 44 patients (61.1%) aged 70 years or older. The re-TURB group had 65 patients (56.5%) aged under 70 years and 50 patients (43.5%) aged 70 years or older (p=0.019). The 2021 EAU guideline states that an age of 70 years or older is a clinical risk factor for NMIBC [7]. In our study, although the no re-TURB group had a higher percentage of older individuals, there were no significant differences in the risk for bladder cancer recurrence in the univariate and multivariate analyses.

The WHO defines a body mass index (BMI; in kg/m^2) of 18.5 or lower as underweight, 18.5 to 24.9 as normal, 25 to 29.9 as overweight, and 30 or higher as obese [14]. In this study, patients in the no re-TURB and re-TURB groups had a normal BMI, with mean BMIs of 24.2±3.1 kg/m^2 and 24.6±3.8 kg/m^2, respectively; there was no significant difference in mean BMI between the two groups (p=0.442). Regarding the presence of underlying disease, 10 patients (13.9%) in the no re-TURB group and 29 (25.2%) in the re-TURB group had diabetes mellitus; 31 patients (43.1%) in the no re-TURB group and 56 (48.7%) in the re-TURB group had hypertension. There were no significant differences in underlying disease between the two groups (p=0.064 and p=0.452, respectively).

Smoking status is known to significantly predict bladder cancer, and the EAU guidelines recommend smoking cessation for patients with bladder cancer [7]. In this study, participants were divided into three groups according to their smoking status (nonsmoker, ex-smoker, and current smoker). Of the 72 patients in the no re-TURB group, 43 (59.7%), 16 (22.2%), and 13 (18.1%) patients were non-smokers, ex-smokers, and current-smokers, respectively. Of the 115 patients in the re-TURB group, 72 (62.6%), 20 (17.4%), and 23 (20%) patients were non-smokers, ex-smokers, and current-smokers, respectively, with no significant differences between the two groups (p=0.937).

The Charlson Comorbidity Index (CCI) predicts the 10-year mortality for patients with a range of comorbid conditions. A CCI of 1 to 2 is considered mild, 3 to 4 is moderate, and 5 or higher is severe. There were no cases with a CCI of 5 or higher in this study, and the patients were divided according to CCI into groups of 0, 1, 2, or ≥3. The number of patients in these categories was 39 (54.2%), 9 (12.5%), 16 (22.2%), and 8 (11.1%), respectively, in the no re-TURB group, and 62 (53.9%), 22 (19.1%), 16 (13.9%), and 15 (13.0%), respectively, in the re-TURB group; there were no significant differences between the two groups (p=0.799) (Table 1).

Table 1. Clinical features of the patients

Variable	No re-TURB group (n=72)	re-TURB group (n=115)	p-value
Sex			0.577
Male	64 (88.9)	99 (86.1)	
Female	8 (11.1)	16 (13.9)	
Age (y)			0.019
<70	28 (38.9)	65 (56.5)	
≥70	44 (61.1)	50 (43.5)	
Body mass index (kg/m^2)	24.2±3.1	24.6±3.8	0.442
Diabetes mellitus	10 (13.9)	29 (25.2)	0.064
Hypertension	31 (43.1)	56 (48.7)	0.452
Smoking			0.937
Non-smoker	43 (59.7)	72 (62.6)	
Ex-smoker	16 (22.2)	20 (17.4)	
Current-smoker	13 (18.1)	23 (20.0)	
CCI			0.799
0	39 (54.2)	62 (53.9)	
1	9 (12.5)	22 (19.1)	
2	16 (22.2)	16 (13.9)	
≥3	8 (11.1)	15 (13.0)	

Values are presented as number (%) or mean±standard deviation.
re-TURB, secondary transurethral resection of the bladder; CCI, Charlson Comorbidity Index.

The 2021 EAU guideline states that tumor diameter ≥3 cm and multiple tumors are clinical risk factors for NMIBC [7]. In the no re-TURB group, 38 patients (52.8%) had tumors <3 cm, and 34 (42.7%) had tumors ≥3 cm. In the re-TURB group, 77 patients (67.0%) had tumors <3 cm, and 38 (33.0%) had tumors ≥3 cm. There were no significant differences in tumor size between the two groups (p=0.053). Patients were divided according to the number of tumors into groups with a single, 2 to 7, and ≥8 tumors. There were no significant differences in the number of tumors between the no re-TURB group (26 [36.1%], 31 [43.1%], and 15 [20.8%], respectively) and the re-TURB group (56 [48.7%], 34 [29.6%], and 25 [21.7%], respectively) (p=0.140) (Table 2).

Remaining tumor was found in 40 cases (34.8%) in the re-TURB group, except in 2 cases (1.7%) of unknown malignant potential. The distribution of tumor stage was Tis in 13 patients (11.3%), low-grade Ta in 9 patients (7.8%), high-grade Ta in 9 patients (7.8%), high-grade T1 in 3 cases (2.6%), high-grade Ta+Tis in 4 cases (3.5%), and high-grade T1+Tis in 2 cases (1.7%). Five patients in the re-TURB group were upstaged to high-grade T1, and including patients diagnosed

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Table 2. Characteristics at the initial TURB

Variable	No re-TURB group (n=72)	re-TURB group (n=115)	p-value
Diameter (cm)			0.053
<3	38 (52.8)	77 (67.0)	
≥3	34 (47.2)	38 (33.0)	
Number of tumors			0.140
1	26 (36.1)	56 (48.7)	
2–7	31 (43.1)	34 (29.6)	
≥8	15 (20.8)	25 (21.7)	

Values are presented as number (%).
TURB, transurethral resection of the bladder; re-TURB, secondary TURB.

Table 3. Stage distribution as assessed during re-TURB

Variable	Value (n=115)
Chronic inflammation	73 (63.5)
UPUMP	2 (1.7)
Tis	13 (11.3)
Ta Low-grade	9 (7.8)
Ta High-grade	9 (7.8)
T1 High-grade	3 (2.6)
T1 High-grade+Tis	2 (1.7)
Ta High-grade+Tis	4 (3.5)

Values are presented as number (%).
re-TURB, secondary transurethral resection of the bladder; UPUMP, urothelial proliferation of unknown malignant potential.

with Tis, a total of 9 patients had their treatment plan changed according to the stage change (Table 3).

We used Kaplan–Meier survival curves to compare RFS between the no re-TURB and re-TURB groups. The re-TURB group had a significantly higher 2-year RFS than did the no re-TURB group (81.3% vs 60.1%, respectively; p=0.005) (Fig. 1). When these two groups were subdivided according to whether they received BCG instillation, in the subgroup that received BCG instillation, the patients who underwent re-TURB had a higher 2-year RFS than did the patients who did not undergo re-TURB (81.7% vs 61.8%, respectively; p=0.004) (Supplementary Fig. 1). However, in the subgroup with no BCG instillation, there was no significant difference in 2-year RFS between patients who did or did not undergo re-TURB (66.7% vs 67.6%, respectively) (Supplementary Fig. 2).

Whether patients underwent re-TURB was the only significant predictor of risk for bladder cancer recurrence, in both the univariate analysis (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.27–0.98; p=0.044) and the multivariate analysis (HR, 0.41; 95% CI, 0.19–0.97; p=0.041). The re-TURB group had a decreased risk of recurrence. Both Cox regression univariate analysis and multivariate analysis

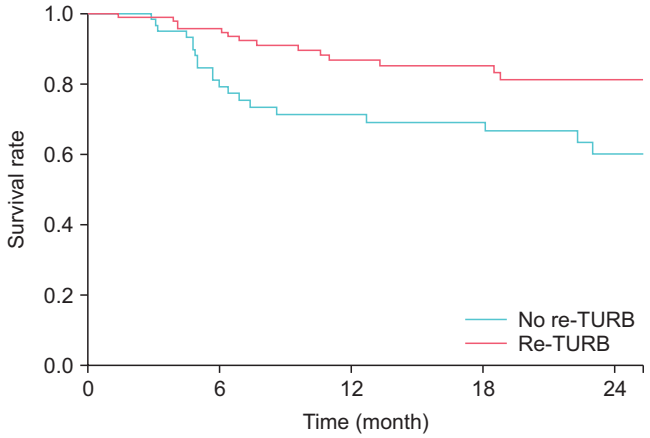

Fig. 1. Comparison of recurrence-free survival between groups that did or did not undergo secondary transurethral resection of the bladder (re-TURB vs. no re-TURB). Total number of patients with high-grade Ta at initial TURB: 187; no re-TURB group: 72; re-TURB group: 115. The vertical dotted line shows the percentage of patients, and the horizontal dotted line is time in months (p=0.005).

revealed that sex, age, BMI, diabetes mellitus, hypertension, smoking, tumor size, tumor multiplicity, and BCG instillation were not significantly associated with bladder cancer recurrence (Table 4). Nevertheless, 2 patients (2.8%) in the no re-TURB group underwent radical cystectomy due to progression (p=0.072) (Supplementary Table).

DISCUSSION

We compared the outcomes of patients with high-grade Ta tumors who did and did not undergo re-TURB. We found that the HR for recurrence was 0.42 times lower, and 2-year RFS was higher (81.3% vs. 60.1%, respectively; p=0.005), among patients with high-grade Ta tumors who underwent re-TURB than among those who did not (Fig. 1). Biopsy results showed that 40 patients in the re-TURB group had remaining tumors. Of 22 patients who had to change their treatment plans because of upstaging, high-grade T1 tumors were identified in 3 patients, high-grade T1 with Tis in 2 patients, Tis in 13 patients, and high-grade Ta with Tis in 4 patients. Of these 22 patients, 2 underwent intravesical therapy with mitomycin C and doxorubicin, and the remaining 20 patients underwent BCG therapy. In the no re-TURB group, 2 patients underwent radical cystectomy. Of these two patients, one underwent radical cystectomy because bladder cancer recurred, and after TURB, the patient was diagnosed with a high-grade T2 tumor. The other patient underwent radical cystectomy because bladder cancer recurred, and the patient was not responsive to BCG.

Many studies have assessed patients with T1 tumors, possibly because of the high recurrence and progression rate

Table 4. Results of the univariate and multivariate analysis by Cox regression to predict risk for bladder cancer recurrence

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex	1.02	0.39–2.62	0.974	1.17	0.37–3.66	0.788
Age	0.86	0.45–1.64	0.645	1.63	0.73–3.67	0.236
re-TURB	0.52	0.27–0.98	0.044	0.41	0.19–0.97	0.041
Body mass index	0.98	0.90–1.06	0.562	1.00	0.90–1.10	0.969
Diabetes mellitus	1.85	0.87–3.95	0.112	0.43	0.17–1.09	0.076
Hypertension	1.13	0.60–2.15	0.705	1.05	0.52–2.11	0.893
Smoking			0.633			0.720
Ex-smoker	1.28	0.58–2.80	0.540	1.48	0.57–3.87	0.421
Current-smoker	0.79	0.34–1.85	0.582	1.37	0.46–4.12	0.574
Diameter	1.82	0.94–3.54	0.076	0.70	0.34–1.45	0.340
Number of tumors			0.504			0.690
2–7	1.51	0.72–3.19	0.276	0.66	0.26–1.70	0.389
≥8	1.44	0.64–3.25	0.381	0.77	0.28–2.09	0.603
BCG	0.87	0.38–1.98	0.740	1.13	0.43–2.97	0.798

re-TURB, secondary transurethral resection of the bladder; HR, hazard ratio; CI, confidence interval; BCG, bacille Calmette–Guérin.

of T1 tumors and the dramatic changes to treatment goals based on whether the bladder can be conserved. However, recurrence and progression rates are not low among patients with Ta tumors. According to the study by Herr [15], 22 patients in the low-grade Ta group (95%) had 15-year progression-free survival, whereas the progression-free survival and disease-specific survival rates were markedly lower in the high-grade Ta group (61% and 74%, respectively). Furthermore, a study by Quhal et al. [16] reported that of 285 patients with TaG3 without Tis, 21 (7.4%) progressed to pT1 and 9 (3.2%) progressed to T2 or higher disease.

For these reasons, some studies have argued that re-TURB is essential for high-grade Ta tumors. Lazica et al. [17] reported that of 142 patients with high-grade Ta during the initial TURB, 36 (41.4%) had tumors confirmed in the re-TURB pathology, 5 of whom (5.7%) were upstaged to T1. However, the major focus of this study was to examine tumor multiplicity at the initial TURB and residual tumor after the initial TURB. Of 36 patients confirmed with tumors during the re-TURB, 27 (55.1%) initially had multifocal tumors, and 28 (77.8%) had tumors confirmed in the re-TURB pathology, including at the initial TURB site. Tumors in the primary site are reconfirmed during re-TURB for high-grade Ta tumors, and therefore, the guidelines concluded that re-TURB should be performed for patients with high-grade Ta tumors [17]. In our study, none of the patients were upstaged to T2 or higher, but 5 of 115 patients (4.3%) were upstaged during the second pathologic examination, showing a similar rate of upstaging to previous studies. However, we confirmed that re-TURB can significantly lower the recurrence rate for initially high-grade Ta tumors regardless of tumor multiplicity. Another study observed a higher rate of tumor upstaging. Herr [18] reported that 114 of 150 patients (76%) who underwent re-TURB had residual tumors, and 28 of 96 patients (29%) who had superficial (Ta, Tis, and T1) bladder tumors were upstaged to an invasive tumor. Fifty patients (33%) had their treatment plans changed after re-TURB, showing that residual tumors were found after the initial TURB for many patients; hence, routine re-TURB was recommended to achieve a better prognosis. As previously mentioned, this study included all patients with high-grade NMIBC tumors instead of examining patients with high-grade Ta tumors separately; therefore, our findings do not provide evidence supporting re-TURB for high-grade Ta tumors [18].

Some studies have reported the limitations of re-TURB for high-grade Ta tumors. Brausi [19] reported that re-TURB should be performed for patients with NMIBC only in limited circumstances, such as if the initial TURB does not show muscle tissue in the specimen, if data obtained from another facility are inadequate, or if bladder-sparing procedures are being considered. Ayati et al. [20] examined residual disease and upstaging after re-TURB in 107 patients with pT1/high-grade Ta (103/4 patients). Twenty-nine patients (27%) had residual tumors, and 11 (10.3%) were upstaged. In that study, multivariate logistic regression confirmed that the presence of muscle in the initial TURB specimen was a significant predictor of upstaging (odds ratio [OR], 8.123; 95% CI, 1.478–44.632). In addition, tumor size (OR, 13.573; 95% CI, 3.104–59.359) and presence of muscle (OR, 21.214; 95% CI,

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6.062–74.244) were significant independent predictors of residual disease at re-TURB. Based on these results, the authors concluded that re-TURB has limited implications for patients who undergo complete initial resection [20].

Studies exclusively assessing high-grade Ta tumors and the latest research on changes in prognosis after re-TURB are lacking. While a few studies have assessed high-grade Ta tumors, most recommend re-TURB after assessing the residual tumor, recurrence, and progression due to incomplete resection, with no studies specifically examining the need for re-TURB for high-grade Ta tumors after complete initial TURB. In particular, no previous study compared the outcomes of patients who did and did not undergo re-TURB. Thus, this study is significant in that it compared the recurrence rate in relation to re-TURB after an initial diagnosis of high-grade Ta tumor between the two groups with no significant differences in clinical risk factors and those who had their visible lesions completely resected.

However, this study had a few limitations. As only patient data from 2016 to 2019 were included, long-term follow-up results were lacking, and the recurrence rate was observed for only a short period of 2 years. Furthermore, we could not compare disease-specific mortality owing to the short follow-up period, and our study included only a small number of patients. Thus, the results might differ in a multicenter study conducted on a large study population. Despite these limitations, this is the first study to perform follow-up on the recurrence rate according to re-TURB in only patients with high-grade Ta tumors, and further studies are required to build on our findings.

CONCLUSIONS

When performing re-TURB for high-grade Ta bladder cancer, additional removal of the residual tumor was beneficial. Additionally, when patients with high-grade Ta bladder tumors did not undergo re-TURB, the risk for bladder cancer recurrence was significantly increased. These findings suggest that re-TURB should be performed in patients with high-grade Ta bladder cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Kyeongchae Lee. Data acquisition: Sang-Hyun Yoo. Statistical analysis: Kyeongchae Lee. Data analysis and interpretation: Kyeongchae Lee. Drafting of the manuscript: Kyeongchae Lee. Critical revision of the manuscript: Seung-hwan Jeong. Administrative, technical, or material support: Seung-hwan Jeong and Sang-Hyun Yoo. Supervision: Ja Hyeon Ku. Approval of the final manuscript: Ja Hyeon Ku.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20210314.

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